(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/047718 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/IB2003/005194

(22) International Filing Date:
17 November 2003 (17.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1054/MUM/2002
28 November 2002 (28.11.2002) IN

(71) Applicant *(for all designated States except US)*: **THEMIS LABORATORIES PRIVATE LIMITED** [IN/IN]; Unit No. S-4 Khira Industrial Estate, B.M. Bhargava Road, Santacruz (West), Mumbai 400 054, Maharashtra State (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANTARKAR, Amit, Krishna** [IN/IN]; House No. C/4, Rani Laxmi Nagar, Nagpur 440 022, State of Maharashtra (IN). **LALA, Rajendra, Ghanshamlal** [IN/IN]; House No. 100, "Guru Cottage", Inlaks Hospital Road, Chembur, Mumbai 400 074, State of Maharashtra (IN). **VARDAM, Poonam, Prakash** [IN/IN]; Devdaya Nagar, Building No. 17, Flat No. 202, Pokhran Road No. 1,, Thane (West)- 400 606, State of Maharashtra (IN). **SHAH, Maya, Janak** [IN/IN]; Saujanya, 3RD N.S Road, Vallabhnagar Society, Vile Parle (West), Mumbai 400 056, Maharashtra (IN).

(74) Agent: **GANGULI, Prabuddha**; Vision - IPR, 103B Senate, Lokhandwala Township, Akurli Road, Kandivali East, Mumbai 400 101, State of Maharashtra (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *of inventorship (Rule 4.17(iv)) for US only*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: PROCESS FOR MANUFACTURING SUSTAINED RELEASE MICROBEADS CONTAINING VENLAFAXINE HCI

(57) Abstract: The present invention relates to viable continuous process for manufacture of agglomeration free, high yield (generally atleast about 95% w/w), uniformly shaped and sized, stable novel pharmaceutical composition of adequate strength comprising upto about 70%w/w of Venlafaxine or its pharmaceutical acceptable salt which is free of organic acid for once a day dosing. Sustained release composition comprising of Venlafaxine HCI provides pH independent release of Venlafaxine HCI atleast for a period of 10 hours without any latent period and can be encapsulated in smallest capsule size 5 for therapeutic effective of Venlafaxine thus providing patient easy to consume dosage form.

WO 2004/047718 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Process for manufacturing sustained release microbeads containing Venlafaxine HCl

Field of invention:

This invention relates to a process for manufacturing stable, novel sustained release compositions comprising of Venlafaxine or its pharmaceutically acceptable salt for once a day dosing.

Background of the Invention:

Venlafaxine HCl, an anti-depressant agent is recommended for a variety of disease and disorders including manic disorder, attention deficit disorder, Parkinson's disease, epilepsy, etc. The recommended daily dose for adults ranges form 75 – 350mg daily in divided doses of two to three times a day. Multiple dosing is inconvenient to patients. It is desirable to minimize the dosage frequency by tailoring sustained release composition specific to a drug, based on desired pharmacokinetic and pharmacodynamic activity.

Venlafaxine HCl, being highly water-soluble has a potential problem of dose dumping and burst effect from a controlled release matrix and hence matrix delivery system is not suitable for consistent and prolonged delivery of the drug to the site of action. It is therefore essential to develop dosage forms to ensure consistent delivery and prolonged plasma levels with insignificant contribution to the initial release in case of a failure of the system, thereby avoiding dose dumping.

Several methods are known in prior art to deposit Venlafaxine HCl on inert cores, further coated with one or more polymeric layers to overcome the problems of matrix delivery system.

PCT publication WO 02/102129 describes programmed release composition comprising 10 – 80% w/w of Venlafaxine HCl. Micronized Venlafaxine HCl is deposited on inert core using PVP alcoholic solution in coating pan to obtain microgranules. Microgranules are coated with talc using PVP solution further coated with plasticized ethylcellulose solution. The yield is not more than 92% w/w. This process requires periodically powdering the product with talc to diminish the static load, thereby interrupting the continuity of process, making it unsuitable for industrial application. The microgranules obtained are not of adequate strength as mechanical condition in fluid bed processor during coating process caused rupturing of some of the microgranules further reducing the yield of the process.

PCT Publication WO 03/041692 deals with extended release composition comprising Venlafaxine HCl (30 – 60% by weight) in which Venlafaxine HCl is coated

with binder (0.5 – 10% by weight) on inert core. This coated core is coated with isolating layer, further coated with polymer layer. The process utilizes water, ethanol or its mixture as a solvent for spraying Venlafaxine HCl. Process utilizing water for spraying Venlafaxine HCl as described therein will results in settling of product mass in product container thereby interrupting the continuity of the process. Process utilizing ethanol as described herein is not sufficient to dissolve Venlafaxine HCl. Venlafaxine HCl suspension in ethanol when sprayed on inert core utilizing PVP as binder (0.5 – 10% by weight) will results in improper fluidization or change in fluidization pattern during the process, leading to inefficient loading of Venlafaxine HCl on inert seeds resulting in drug loss and low batch yield. The yield of this process is generally not more than 95%w/w.

PCT Publication WO 0071099 describes a multiparticulate controlled release formulation of selective serotonin reuptake inhibitor (SSRI) such as fluvoxamine. The process comprises deposition of SSRI, organic acid and polymeric material on inert core to obtain drug-loaded beads. These are coated with rate controlling membrane ammonio methacrylate co-polymer, dibutyl sebacate and talc. However, use of organic acid with Venlafaxine HCl is not advisable. Moreover, organic acid may influence the physiochemical properties of the rate controlling membrane, thereby affecting the stability of such formulation.

None of the prior art teaches a economical and continuous process for manufacture of agglomeration free, high yield (generally atleast about 95% w/w), uniformly shaped and sized, stable novel pharmaceutical composition of adequate strength comprising upto about 70%w/w of Venlafaxine HCl which is free of organic acid for once a day dosing.

Venlafaxine HCl is more soluble in water as compared to that in alcohol and hence would be a solvent of preferred choice. Such an approach would substantially reduce the processing time and cost, making the process viable. However it is known that Venlafaxine HCl develops tack and static charge during its deposition on inert seeds by powder layering using aqueous binder solution. This tendency of developing tackiness and static charge increases when Venlafaxine HCl is sprayed from an aqueous or hydroalcoholic binder solution or dispersion on inert seeds. This problem of tackiness and static charge leads to further processing problems such as

- Agglomeration of drug coated seeds.
- Improper fluidization or change in fluidization pattern during the process, leading to inefficient loading of Venlafaxine HCl on inert seeds resulting in drug loss and low batch yield.

- Settling of the product mass in the product container thereby interrupting the continuity of the process.

The above-mentioned problems are especially witnessed when equipment such as fluid bed bottom spray processor or coating pan is used.

Summary of the Invention:

The object of the present invention is to provide a viable continuous process for manufacture of agglomeration free, high yield (generally atleast about 95% w/w), uniformly shaped and sized, stable novel pharmaceutical composition of adequate strength comprising upto about 70%w/w of Venlafaxine or its pharmaceutical acceptable salt which is free of organic acid for once a day dosing.

Another object of the invention is to provide a continuous process utilizing water as a solvent for spraying Venlafaxine HCl unlike alcohol as described in prior art.

Another object of the invention is to provide a continuous process, which is consistent with proper fluidization pattern.

Another object of the invention is to provide a process for manufacture of novel sustained release compositions comprising of Venlafaxine HCl which when tested in vitro provides pH independent release of Venlafaxine HCl atleast for a period of 10 hours without any latent period.

Another object of the invention is to provide a process for manufacture of novel sustained release compositions comprising Venlafaxine HCl, which can be encapsulated in smallest capsule size 5 for therapeutic effective amount of Venlafaxine thus providing patient easy to consume dosage form.

Another object of the invention is to provide a process for manufacture of novel sustained release composition comprising of Venlafaxine HCl without the problems of dose dumping and burst effect from the formulation.

Description of the invention:

As indicated in the background of the invention there are several problems such as tackiness, static charge, agglomeration, improper fluidization and settling of product mass during processing Venlafaxine HCl in aqueous media. It has surprisingly been found that the above-mentioned problems are solved,

- When Venlafaxine HCl is sprayed on inert seeds along with binder preferably hydroxypropylmethylcellulose (HPMC) in concentration of atleast about 35%w/w along with antitack agent preferably talc in the concentration of atleast about 10.5 %w/w of Venlafaxine HCl or

- When Venlafaxine HCl is deposited on inert seeds along with antitack agent such as talc and inert excipient such as starch using binder preferably in the concentration of less than about 2.5 %w/w.

Yield of the process of this invention is not less than about 95%w/w.

Thus the present invention provides a viable continuous process for manufacture of stable novel sustained release pharmaceutical composition comprising upto about 70%w/w of Venlafaxine or its pharmaceutical acceptable salt preferably Venlafaxine HCl for once a day dosing, where Venlafaxine HCl is processed in aqueous media and is free of organic acid.

In one of the embodiments of the invention, sustained release pharmaceutical composition processed in aqueous medium is in the form of agglomeration free, uniformly shaped and sized microbeads of adequate strength. The yield of the process of the present invention is atleast about 95%w/w and mostly about 97%w/w.

The sustained release composition comprising Venlafaxine HCl is capable of being filled into capsule for therapeutic effective amount of Venlafaxine. Sustained release composition comprising of Venlafaxine HCl is even capable of being filled in smallest capsule of size '5' for ease of administration and patient acceptance.

The formulation of the present invention comprises sustained release composition comprising therapeutically effective amount of Venlafaxine.

More particularly, the sustained release formulation of the present invention comprises of Venlafaxine HCl, binder, antitack agent optionally along with inert excipient layered or coated on inert seeds from aqueous media, further optionally coated with antitack agent and non-functional polymer, further coated with a functional polymer and plasticizer.

In another embodiment of this invention, sustained release composition comprising of Venlafaxine HCl comprises alternate layer of admixture of Venlafaxine HCl, inert excipient and antitack agent with binder preferably hydroxypropylmethylcellulose on inert seeds in aqueous media, which are coated with antitack agent and non-functional polymer, further coated with a functional polymer and plasticizer. Unlike the process disclosed in PCT publication WO 02/102129 the process of the present invention

- Does not require powdering the product with talc for diminishing the static load.
- Has higher yield above about 95%w/w and mostly above about 97%w/w.
- Does not cause rupturing of microbeads during the coating process indicating that microbeads obtained are of adequate strength.

In another embodiment of the invention, sustained release composition comprising of Venlafaxine HCl comprises inert seeds coated with Venlafaxine HCl, antitack agent and binder preferably hydroxypropylmethylcellulose from aqueous media, further coated with a functional polymer and plasticizer. This is structurally different in comparison with PCT publication WO 03/041692, as it does not require drug cores to be coated with the isolating / protecting / separating layer.

Detailed Description of the Invention:

This invention provides a process for the preparation of sustained release composition comprising of Venlafaxine or its pharmaceutically acceptable salt preferably Venlafaxine HCl on inert seeds wherein Venlafaxine HCl is processed in aqueous media. The invention involves 2 sequential stages for the preparation of sustained release composition comprising of Venlafaxine HCl.

Stage I: Preparation of Drug core

Drug core is prepared by depositing Venlafaxine HCl, antitack agent and optionally an inert excipient in aqueous media, as a single layer or as an alternating layer with binder on inert seeds. The drug core so obtained is hardened by optionally coating and / or layering drug core with non-functional polymer and antitack agent in aqueous media as a single layer or alternate layer to obtain hardened drug core.

The process utilizes water as a solvent for depositing Venlafaxine HCl in contrast to alcohol as described in the prior art.

The process described is consistent with the fluidization pattern when Venlafaxine HCl is sprayed form the aqueous media in fluid bed bottom spray coater enabling efficient deposition of Venlafaxine HCl on inert seeds thereby providing high yield.

However, the process described herein for the preparation of the drug core can even utilize alcohol or hydroalcoholic media for depositing Venlafaxine HCl on inert seeds.

In contrast to process in prior art (PCT publication WO 0071099) the process of this invention does not require use of organic acid for tailoring drug release characteristic.

Stage II: Preparation of Sustained release composition

Sustained release composition is prepared by coating drug core or hardened drug core with a combination of functional polymer and plasticizer.

In one of the embodiment of the invention sustained release composition of the present invention is prepared by coating drug core or hardened drug core with a combination of functional polymer, plasticizer and optionally with antitack agent.

Sustained release composition comprising Venlafaxine HCl so obtained exhibits pH independent release profile at least for a period of 10 hours when analyzed in-vitro using USP type II (paddle) dissolution testing apparatus at 100 rpm in 900 ml media at 37°C.

The process is now described in details.

Stage I: Preparation of Drug Core:

Venlafaxine HCl, antitack agent and optionally an inert excipient are mixed to obtain an admixture, which is deposited on inert seeds such as sugar sphere using aqueous binder solution to obtain drug core.

In an embodiment of the invention, Venlafaxine HCl is in admixture with antitack agent and inert excipient.

Admixture of Venlafaxine HCl, antitack agent and inert excipient is deposited on sugar sphere as an alternating layer with binder solution in water.

Alternatively, suspension of Venlafaxine HCl, binder and antitack agent in water where Venlafaxine HCl is in dissolved state can be deposited as a single layer on sugar sphere to obtain drug cores.

The drug core is suitably dried in equipments such as coating pan, tray drier or fluid bed drier or their likes to arrive a moisture content of less than 5%w/w preferably less than 3%w/w and more preferably less than 2%w/w.

The drug core after drying is optionally coated with a layer of non-functional polymer and antitack agent to obtain hardened drug core.

In another embodiment of the invention, non-functional polymer and antitack agent is deposited from aqueous media as a single layer on drug core.

Alternatively, non-functional polymer in water can be deposited with antitack agent as an alternate layer on drug core to obtain hardened drug core. The hardened drug core is suitably dried in equipments such as coating pan, tray drier and fluid bed drier or their likes to arrive a moisture content of less than 5%w/w preferably less than 3%w/w and more preferably less than 2%w/w.

Inert seeds such as sugar sphere comprising of sugar and starch is preferably used. Alternatively inert seeds comprising of microcrystalline cellulose or any other suitable inert material may also be used. The particle size of the sugar sphere used

may be in the range of about 1680 to 300 microns preferably about 1200 to 500 microns.

Antitack agent used in the present invention is selected form the group of talc, colloidal silicon dioxide, magnesium stearate, glyceryl behenate, glyceryl monostearate and their mixtures the preferable choice being talc with or without colloidal silicon dioxide and are used in the concentration range of about 2.5 – 20% w/w of Venlafaxine HCl.

Inert excipients are selected form the group consisting of starch, lactose, microcrystalline cellulose, low viscosity grade hydroxypropylcellulose, mannitol, pulverized sugar, sorbitol and their likes. Inert excipient may be used alone or in combination and is preferably starch and is used in concentration range of about 2-12%w/w of Venlafaxine HCl.

Binder is selected from the group consisting of cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, polyvinylpyrollidone, sugar, acrylic acid and methacrylic acid copolymer. Binder may be used alone or in combination and is preferably hydroxypropylmethylcellulose used in the concentration upto about 55% w/w of Venlafaxine HCl.

Non-functional polymer is selected form the group consisting of cellulose derivatives like hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrollidone, sugar, acrylic acid and methacrylic acid copolymer and is used in the concentration of upto about 5%w/w of drug core.

Hydroxypropylmethylcellulose preferably used as a binder and as non-functional polymer has a nominal viscosity of about 3 – 15 cps when measured as 2% solution in water at 20°C.

Although the solvent of preferred choice for processing Venlafaxine HCl is water, other solvents such as alcohol, hydroalcoholic mixture, organic solvent or their mixtures can also be used.

Stage II: Preparation of Sustained Release Composition:

Drug core or hardened drug core so obtained as described in stage I is coated with a combination of functional polymer, plasticizer and optionally antitack agent to obtain sustained release composition. The functional polymer for coating may be used alone or in combination in the range of 1 – 25% w/w of drug core or hardened drug core.

Functional Polymer used for coating drug core or hardened drug core is selected from the group of methacrylic acid copolymer, cellulose derivatives preferably alkyl

cellulose such as ethylcellulose hydroxypropylmethylcellulose, alone or in combination and is preferably ethylcellulose. Ready to use aqueous dispersion of ethylcellulose may also be used as a functional polymer for the preparation of sustained release composition.

Ethylcellulose used as functional polymer for sustaining the release of Venlafaxine HCl has a nominal viscosity of about 9 – 11 cps when measured as a 5% w/w solution in toluene: alcohol (80:20) at 25°C.

Plasticizer used is selected from the group of hydrophobic and hydrophilic plasticizer and preferably is triacetin and triethylcitrate and is used in the concentration of about 5 – 25%w/w preferably about 10 – 20% w/w of the functional polymer.

Optionally antitack agent such as talc may also be added in the concentration of upto about 30%w/w of the functional polymer preferably when aqueous dispersion comprising of functional polymer is used.

The process described herein may be carried out completely or in part in aqueous or non-aqueous media such as methanol, ethanol, isopropanol or their mixtures.

The above process can be carried out in equipment such as fluid bed bottom spray processor, coating pan and their likes. The process described can be carried out using single equipment either fluid bed bottom spray processor or coating pan or involves use of both equipments. The process of the invention described herein is the viable continuous process for the preparation of sustained release composition comprising of Venlafaxine HCl.

The invention is now described with non – limiting examples for the preparation of sustained release microbeads comprising Venlafaxine HCl.

Example 1 – 3:

I) Preparation of Drug Core:

Venlafaxine HCl was passed through 200 mesh ASTM and mixed with starch and talc in planetary mixer for about 10 minutes. HPMC E05 was dispersed and dissolved in water. The concentration of HPMC in water can be upto about 10%w/w. Sugar sphere were loaded in coating pan. HPMC solution was sprayed on sugar sphere. When desired level of wetting was observed, the admixture of Venlafaxine HCl, starch and talc was layered till the wetted agglomerated sugar sphere were unagglomerated. This operation was repeated until the total quantity of admixture was used up. Thereafter, the drug cores were dried in tray drier. They are then sieved through desired mesh and checked for moisture content and particle size. The drug

core of undesirable size (utilizable residue) that was retained above and below the desired mesh was mixed with water and was added to nonfunctional polymer suspension containing talc. The suspension was filtered through appropriate mesh and was sprayed on drug cores in coating pan to obtain hardened drug core. The solid content of this suspension in water may be upto 20% w/w. These hardened drug cores were dried in tray drier and checked for moisture content and particle size.

II) Preparation of Sustained Release Microbeads:

Ethyl cellulose was dispersed and dissolved in the mixture of methanol and methylene chloride (2:3). Triacetin was added to this solution. The solution was filtered through appropriate mesh and was sprayed of hardened drug core in fluid bed bottom spray processor to obtain sustained release microbeads. Other organic solvents such as isopropanol, acetone can also be used. Methanol and methylene chloride may be used in the ratio 1:9 to 9:1 preferably in the ratio of 2:3. Aqueous ready to use dispersion of ethylcellulose can also be used. The solid content of the dispersion or solution used should not be more than about 20%w/w.

The processing parameters during the coating process was adjusted to have an inlet air temperature of about 20°C to about 60°C, preferably about 30°C to 45°C outlet air temperature of about 20°C to about 45°C preferably 25°C to 40°C, atomization air pressure of about 0.8 - 3.5 bars, fluidization flap open from about 15 to about 90% w/w. Sustained release microbeads are dried in the same equipment maintaining the inlet temperature between about 50-80°C and outlet temperature between about 40 - 60°C to have moisture content of less than 5% and preferably less than 3% and more preferably less than 2%w/w. Alternatively the coating may also be carried out in coating pan to obtain sustained release microbeads comprising of Venlafaxine HCl.

Ingredients	**% w/w**	**% w/w**	**% w/w**
I) Drug Core	**Ex 1**	**Ex 2**	**Ex 3**
Venlafaxine HCl	16.60	33.39	56.89
Sugar sphere	66.42	48.25	22.71
Starch	1.66	0.83	2.00
Talc	2.49	1.67	3.00
HPMC E05	0.33	0.42	1.50
Hardened Drug Core			
HPMC E05	1.31	1.33	1.72
Talc	0.39	0.40	0.52

II) Sustained Release Microbeads			
Ethyl Cellulose	9.82	12.47	10.60
Triacetin	0.98	1.24	1.06
Total	**100**	**100**	**100**
Particle size of sugar sphere	18 –20 # ASTM	20–22 # ASTM	25 – 30 # ASTM

Example 4:

I) Preparation of Drug Core:

HPMC E05 was dispersed and dissolved in water. Venlafaxine HCl was dissolved in water. The solutions were mixed and talc was added. The solution was filtered through appropriate mesh and was sprayed on sugar sphere in fluid bed bottom spray processor with inlet air temperature between about 50 - 80°C, outlet air temperature about 40 - 55°C, atomization air pressure about 0.8 - 3.5 bars, fluidization flap open between about 15 - 90%. After spraying this drug suspension, the drug cores were dried in the same equipment maintaining the inlet temperature between about 50-80°C and outlet temperature between about 40 - 60°C to have moisture content of less than 5% and preferably less than 3% and more preferably less than 2%w/w. The total solid content in the spray suspension was upto about 30% w/w.

II) Preparation of Sustained Release Microbeads:

The process of coating of drug core after drying in fluid bed bottom spray processor was continued as described in example 1 – 3 to obtain sustained release microbeads comprising of Venlafaxine HCl.

The yield of the process is not less than 95%w/w and is generally greater than about 97%w/w.

Ingredients	% w/w
I) Drug Core	
Venlafaxine HCl	39.22
Sugar sphere (18 – 20 # ASTM)	25.37
Talc	5.88
HPMC E05	19.61

II) Sustained Release Microbeads

Ethyl Cellulose	9.01
Triacetin	0.91
Total	**100**

Sustained release microbeads comprising of Venlafaxine HCl prepared in various strength as illustrated above are capable of being filled in various size capsule viz size 0 – size 5 for various dose range i.e. 37.5 mg, 75mg and 150mg of Venlafaxine. Sustained release microbeads comprising of Venlafaxine HCl are capable of being filled in smallest capsule of size '5' for the dose of 37.5mg of Venlafaxine for ease of administration and patient acceptance.

Dissolution Studies:

The performance of the sustained release microbeads comprising of Venlafaxine HCl monitored by vitro dissolution testing using USP type II (paddle) apparatus at 100 rpm in 900 ml distilled water / 0.1 N HCl / pH 4.5 acetate buffer / pH 6.8 phosphate buffer / pH 7.2 phosphate buffer at 37°C. The acceptance criteria for any batch of sustained release microbeads comprising Venlafaxine HCl is given below:

Time (hours)	Cumulative % drug release
1	NMT 15 %
4	30 % – 50 %
8	55 % - 80 %
10	NLT 65 %

If a batch of sustained release microbeads comprising of Venlafaxine HCl releases the drug too slow to comply with the dissolution release profile of the formulation, a portion of (hardened) drug core or of lower coating level may be added to comply with above mentioned drug release profile.

If a batch of sustained release microbeads comprising of Venlafaxine HCl releases the drug too rapidly, then it may receive an additional coat to comply with desired drug release profile.

Sustained release microbeads comprising of Venlafaxine HCl provides a pH independent in-vitro release of Venlafaxine HCl atleast for a period of 10 hours without any latent period.

The present invention thus provides a process for manufacture of novel sustained release microbeads comprising of Venlafaxine HCl without the problems of dose dumping and burst effect from the formulation.

Bioequivalence Studies:

A randomized two way, two period, two treatment cross over bioequivalence study of Venlafaxine HCl sustained release capsule comprising 150 mg of Venlafaxine HCl (test) was compared with 2 X 75mg extended release capsule (reference) comprising of 75 mg of Venlafaxine HCl in 12 healthy male, adult human volunteers under fasting condition. The results were as follows.

Pharmacokinetic parameters	**Test**	**Reference**
Cmax ng/ml) (mean ± std. dev.)	161.75 (± 12.27)	162.00 (± 17.61)
Tmax (hrs.) (mean ± std. dev.)	3.08 (± 0.35)	3.16 (± 0.32)
AUC (0-30) ng.hr/ml (mean ± std. dev.)	1539.40 (± 249.80)	1565.83 (± 238.02)

Sustained release microbeads comprising of Venlafaxine HCl is bio -equivalent and provides therapeutic blood levels of the Venlafaxine HCl for once a day dosing for therapeutic effective amount of Venlafaxine HCl.

Sustained release microbeads comprising of therapeutic effective amount Venlafaxine HCl is stable atleast for a period of 2 years.

Thus the present invention provides a viable continuous novel process for the manufacture of sustained release composition comprising of upto about 70%w/w of Venlafaxine or its acceptable salt preferably Venlafaxine HCl, wherein

- Venlafaxine HCl is processed in aqueous media unlike alcohol as disclosed in prior art.
- Composition is in the form of agglomeration free, uniformly shaped and sized microbeads of adequate strength for once a day dosing.
- Composition is stable atleast for a period of 2 years and is free of organic acid.
- The yield of the process is high upto about 95%w/w and mostly about 97%w/w.
- The process is a continuous process, which is consistent with the proper fluidization pattern when Venlafaxine HCl is sprayed in fluid bed bottom spray processor utilizing water as a solvent.
- The composition in the form of microbeads provides pH independent in-vitro release of Venlafaxine HCl atleast for a period of 10 hours without any problems of dose dumping and burst effect.

Claims:

We claim:

1. A novel sustained release composition comprising of an inert core, said inert core being coated or layered using aqueous media preferably water with a combination of upto about 70% w/w Venlafaxine or its pharmaceutical acceptable salt, binder, antitack agent and optionally inert excipient to form a drug core, with an optional coat of a combination of non – functional polymer and anti-tack agent in aqueous media preferably water further coated with combination of functional polymer and plasticizer, the composition being free of organic acid.

2. A high yield viable continuous novel process for the preparation of sustained release composition comprising upto about 70% w/w of Venlafaxine or its pharmaceutically acceptable salt preferably Venlafaxine HCl wherein Venlafaxine HCl is being processed in aqueous media preferably water, the process comprises sequential preparation of drug core using aqueous media preferably water followed by optional preparation of hardened drug core using aqueous media preferably water followed by preparation of unagglomerated sustained release microbeads of uniform shape and size exhibiting pH independent in-vitro release of Venlafaxine HCl with no latent period, the composition being free of organic acid.

3. A novel process in aqueous media as claimed in claims 1 and 2, wherein preparation of drug core comprises deposition of Venlafaxine HCl, antitack agent and optionally an inert excipient on inert seeds using aqueous media preferably water as a single layer or as an alternating layer with binder.

4. A novel process in aqueous media as claimed in claims 1 and 2, wherein optional preparation of hardened drug core comprises coating or layering drug core with a combination of non-functional polymer and antitack agent in aqueous media preferably water as a single layer or alternate layer.

5. A novel process in aqueous media as claimed claims 1 and 2, wherein the preparation of sustained release microbeads comprises coating drug core or hardened drug core with combination of functional polymer and plasticizer.

6. A novel composition and process in aqueous media as claimed in claims 1 – 4, wherein binder and an optional non-functional polymer sprayed from the aqueous media preferably water is selected form the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrollidone, sugar, acrylic acid and methacrylic acid copolymer and their mixtures and is preferably hydroxypropylmethylcellulose in the concentration upto about 55% w/w of Venlafaxine HCl.

7. A novel composition and process in aqueous media as claimed in claims 1 – 4, wherein the antitack agent is selected form the group of consisting of talc, colloidal silicon dioxide, magnesium stearate, glyceryl behenate, glyceryl monostearate and their mixtures and is preferably talc in the concentration of about 2.5 – 20% w/w of Venlafaxine HCl.

8. A novel composition and process in aqueous media as claimed in claims 1 – 3, wherein the inert excipients are selected form the group consisting of starch, lactose, microcrystalline cellulose, low viscosity grade hydroxypropylcellulose, mannitol, pulverized sugar, sorbitol and their mixtures and is preferably starch in concentration of about 2- 12%w/w of Venlafaxine HCl.

9. A novel composition and process in aqueous media as claimed in claims 1, 2 and 5 wherein the functional polymer is selected form the group of ethylcellulose hydroxypropylmethylcellulose, methacrylic acid copolymer alone or in combination and is preferably ethylcellulose in the concentration of upto about 25%w/w of drug core or hardened drug core and plasticizer is selected from the group of hydrophilic and hydrophobic plasticizer and is preferably triacetin or triethylcitrate in the concentration of about 5 – 25%w/w preferably about 10 – 20% w/w of the functional polymer.

10. A novel sustained release composition, wherein formulation comprising Venlafaxine HCl comprises blend of upto 100% by weight of sustained release microbeads comprising Venlafaxine HCl and from 0% to about 50%w/w of drug core and / or hardened drug core and / or of lower coating level of sustained release microbeads comprising Venlafaxine HCl.

11. A novel sustained release composition as claimed in claims 1,2 and 10 wherein the pH independent release rate of Venlafaxine HCl from the composition at the end of 1, 4, 8 and 10 hours lies in the range of not more than about 15%, about 30 – 50%, about 55 – 80% and not less than about 65% respectively when measured in-vitro in USP type II apparatus at about 100 rpm in about 900 ml distilled water or 0.1 N HCl or pH 4.5 acetate buffer or pH 6.8 phosphate buffer or pH 7.2 phosphate buffer.

12. A novel process as claimed in any of the preceding claims wherein the process is carried out in single equipments such as fluid bed bottom spray processor or coating pan or both.

13. A novel process in aqueous media as claimed in claims 1 – 3, 10 and 12 wherein processing of Venlafaxine HCl in aqueous media preferably water for preparing drug core, carried out in fluid bed bottom spray processor at inlet air temperature about 50 - 80°C, outlet air temperature about 40 - 55°C, atomization air pressure about 0.8 - 3.5 bars, fluidization flap open between about 15 - 90%.

14. A novel process in aqueous media as claimed in claims 1,2,5,10 and 12 wherein coating of drug core or hardened drug core carried out in fluid bed bottom spray processor at inlet air temperature about 20 - 60°C preferably about 30°C - 45°C, outlet air temperature about 20 - 45°C preferably about 25°C - 40°C, atomization air pressure about 0.8 - 3.5 bars, fluidization flap open between about 15 - 90%.

15. A novel composition and process in aqueous media preferably water as claimed in any of the preceding claims wherein the yield of the process is atleast about 95%w/w and mostly about 97%w/w.

16. A novel sustained release composition as claimed in claims 1,2 10 and 11 wherein the composition comprising Venlafaxine HCl processed as sustained release microbeads is capable of being filled into capsule size 5 to size 0 for a dose of upto about 150 mg of Venlafaxine for once a day dosing.

17. A novel composition and process as claimed in any of the preceding claims wherein water used as aqueous media can be replaced in part or whole with non-aqueous media such as methanol, ethanol, isopropanol or their mixtures.